GLAXO GROUP LTD *WO 2003066632-A1

2002.02.05 2002-002679(+2002GB-002679) *(2003.08.14)* C07D 471/04, A61K 31/40, A61P 25/00

Use of new and known sulfonyl bicyclic heterocyclic compounds for treating e.g. depression, anxiety, Alzheimer's disease, age related cognitive decline and obesity (Eng)

C2003-185665 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW) R(AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW)

Addnl. Data: AHMED M, BROMIDGE S
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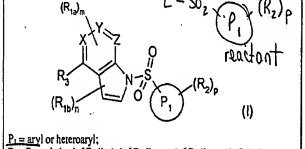
NOVELTY

Sulfonyl bicyclic heterocyclic compounds (I) are used for the treatment or prophylaxis of depression, anxiety, Alzheimer's disease, age related cognitive decline, attention deficit hyperactivity disorder, obesity, mild cognitive impairment and schizophrenia.

DETAILED DESCRIPTION

Sulfonyl bicyclic heterocyclic compounds of formula (I), their salts or solvates, are used for the treatment or prophylaxis of depression, anxiety, Alzheimer's disease, age related cognitive decline, attention deficit hyperactivity disorder, obesity, mild cognitive impairment and schizophrenia.






$P_1$ = aryl or heteroaryl;

$R_{1a}$, $R_{1b}$ = halo, 1-6C alkyl, 1-6C alkoxy, 1-6C alkanoyl, CN, $CF_3$, $OCF_3$, phenyloxy, benzyloxy or 3-6C cycloalkyloxy;

$R_2$ = aryl or heteroaryl (both optionally substituted by $R_{1a}$ and $R_{1b}$), halo, 1-6C alkyl, 3-6C cycloalkyl, 1-6C alkoxy, 1-6C alkylthio, 1-6C alkylsulfinyl, 1-6C alkylsulfonyl, 1-6C alkanoyl, CN, $CF_3$, $OCH_2CF_3$, $OCF_3$, OH, 1-6C hydroxyalkyl, 1-6C hydroxyalkoxy, 1-6C alkoxycarbonyl, 1-6C alkoxy-1-6C alkoxy, $NO_2$, amino, N(1-6C alkyl)$_2$, NH-1-6C alkyl, 1-6C alkylamino, di-1-6C alkylamino, C(O)$OR_a$, $CONR_aR_a$ or $NR_aCOR_a$;

$R_a$-$R_a$ = H or 1-6C alkyl, or

$R_5 + R_6$ = 5-7 membered azacyclic ring optionally containing an additional N, O or S heteroatom;

$R_3$ = 5-7 membered heterocyclyl or bicyclic heterocyclyl containing 1-3 N, S or O heteroatoms (both optionally C and/or N-substituted by at least one 1-6C alkyl);

m, n = 0-4;

p = 0-5; and

X, Y, Z = N or C,

provided that one or two of X, Y and Z is N.

INDEPENDENT CLAIMS are also included for:

(1) new compounds (I), excluding 5-bromo-7-(phenylsulfonyl)-4-(1-piperidinyl)-7H-pyrrolo[2,3-d]pyrimidine and 5-iodo-7-(phenylsulfonyl)-4-(1-piperidinyl)-7H-pyrrolo[2,3-d]pyrimidine, and

(2) preparation of (I).

ACTIVITY

Antidepressant; Tranquilizer; Nootropic; Neuroprotective; Anorectic; Neuroleptic; Anticonvulsant; Antimigraine; Antiparkinsonian; CNS-Gen.; Anabolic; Eating-Disorders-Gen.; Cerebroprotective; Antiaddictive; Antialcoholic; Antismoking.



2003-679528/64

MECHANISM OF ACTION

5-Hydroxytryptamine$_6$ (5-$HT_6$) receptor antagonist..

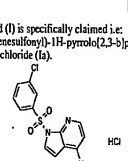
In a test as described in WO98/27081, results showed that 4-[1-(3-chlorobenzenesulfonyl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-piperazine hydrochloride (Ia) exhibited good affinity for the 5-$HT_6$ receptor, having a pKi value of greater than 8 at human cloned 5-$HT_6$ receptors.

USE

Used for the treatment or prophylaxis of depression, anxiety, Alzheimer's disease, age related cognitive decline, attention deficit hyperactivity disorder, obesity, mild cognitive impairment and schizophrenia (all claimed). (I) Are also used for the treatment of epilepsy, obsessive compulsive disorder, migraine, cognitive memory impairment, Parkinson's disease, sleep disorder (e.g. disturbance of circadian rhythm), feeding disorder (e.g. anorexia and bulimia), panic attack, disorders associated with spinal trauma and/or head injury such as hydrocephalus, and withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines.

SPECIFIC COMPOUNDS

One compound (I) is specifically claimed i.e: 4-[1-(3-chlorobenzenesulfonyl)-1H-pyrrolo[2,3-b]pyridin-4-yl]piperazine hydrochloride (Ia).




ADMINISTRATION

The dosage is 0.05-1000 (especially 20-40) mg orally, parenterally or rectally.





(con't)

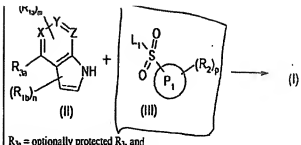
EXAMPLE

t-BuOK (0.15 ml, 1.0 M in tetrahydrofuran (THF)) was added dropwise to an ice cooled solution of 4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-piperazine-1-carboxylic acid tert butyl ester (40 mg) in THF (3 ml) and stirred for 20 minutes. A solution of 3-chlorobenzenesulfonyl chloride (33 mg) in THF (2 ml) was added dropwise and the mixture was warmed to room temperature. Water was added after 3 hours and the mixture extracted by column chromatography to give 4-[1-(3-chlorobenzenesulfonyl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-piperazine-1-carboxylic acid tert butyl ester (30 mg).

This compound (25 mg) was exposed to 20% trifluoroacetic acid in dichloromethane for 1 hour. Evaporation *in vacuo*, treatment with 1M hydrochloric acid in diethylether in the presence of methanol and evaporation *in vacuo* produced 4-[1-(3-chlorobenzenesulfonyl)-1H-pyrrolo[2,3-b]pyridin-4-yl]piperazine hydrochloride (Ia) (19 mg).

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: Preparation of (I) comprises e.g. reacting a bicyclic heterocyclic compound of formula (II) with a sulfonyl compound of formula (III) and optionally deprotecting.




$R_{3a}$ = optionally protected $R_3$, and
$L_1$ = a leaving group, preferably halo.
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